IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

George M. HALOW

Serial No: **10/756,269**

Group Art Unit: **1616**

Examiner: **Frank Choi**

Filed : **January 14, 2004**

For : **BOWEL CLEANSING COMPOSITION**

DECLARATION UNDER 37 CFR §132

I, the inventor in the above-identified application, attest that I contacted the lead author of "Precolonoscopy Bowel Cleansing ...," Gastroent. 122:334, 2002, Dr. Sobrino-Faya, for more detailed information on the bowel cleansing composition described in this Abstract after it was applied by the Examiner in this case. In response, I received the attached letter (Exhibit A) from this author. I was further told by Dr. Sobrino-Faya in a related telephone call that the only publication of the research described in this letter was the Abstract of record in this case.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

George M. Halow

George M. Halow, M.D.

August 3/2006

Date

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REMARKS

Commissioner for Patents
P.O. Box 1450
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Sir:

In a telephone interview between the Examiner and Applicant's undersigned attorney on 1 August 2006 in connection with the Advisory Action, the Examiner indicated that the remaining outstanding issue in this case was the "Spanish reference," i.e., Gastroent. 122:334, 2002, authored by Dr. Sobrino-Faya. The Examiner's stated basis for maintaining this rejection was that the PEG composition as described in this reference did not explicitly state that the composition included balancing electrolytes.

As previously noted by Applicant, to the best of his knowledge, bowel cleansing compositions universally include electrolytes as adjuncts to correct electrolyte imbalances caused by the administration of these compositions. Consequently, the compositions are commonly referred to merely as "PEG compositions" (see, e.g., Exhibit B, Kurume Med. J. 39:117-121, 1992, which describes PEG compositions with electrolytes and thereafter refers to them as "PEG solutions").

As confirmed by Dr. Sobrino-Faya's letter (Exhibit A), the PEG compositions described in his Abstract did include the customary electrolytes.

With respect to Applicant's Amendment Under 37 C.F.R. §116, claims 1, 13, and 37 were amended pursuant to the interview of 5 May 2006, which included a discussion of the proposed amendments to these claims as reflected in Applicant's §116 Amendment. Applicant's Response to the Advisory Action deletes claims 54-56 following the Examiner's objection to these claims.

The letter from Dr. Sobrino-Faya was not earlier submitted as it is not prior art, and it only became an issue when the Examiner challenged the meaning of the term "PEG solution" in the Sobrino-Faya Abstract of record after Applicant's §116 Amendment was filed.

Accordingly, entry of the §116 Amendment, as revised, and reconsideration of the outstanding rejection in view of Applicant's amendments are remarks therein, and the present Declaration, with its attendant Exhibits and Remarks, is earnestly requested.

It is believed that the application is in condition for allowance, and such action is also requested.

Respectfully submitted,

Jean A. Buttmi
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August 3, 2006

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October 14, 2005

Dear Dr. Halow:

We considered that oral sodium phosphate (NaP) (Fosfosoda®, 2 bottles with 45 ml, each of them containing 10.8 g of sodium biphosphate and 24.4 g of sodium phosphate) appeared to be better tolerated than standard polyethylene glycol (PEG) solution, containing electrolytes, (Movicol®, powder sachets, each containing 13.8g polietilenglicol 3350 and electrolytes: sodium 65 mM, chloride 53 mM, potassium 5,4 mM, bicarbonate 17 mM) in the preparation of patients for colonoscopy because of the much smaller volume to be ingested. On the contrary, safety of NaP could be limited by the risk of serum electrolyte imbalance. We hypothesized that the association of half dose of both NaP and PEG preparations could improve the safety of NaP as well as the tolerance to PEG while maintaining the cleansing effectiveness. One hundred and five out-patients patients were prospectively randomized to receive one of three preparations in a single-blind study. Group 1 (34 patients) received 3 liters of PEG solution (18 sachets dissolved in 3 liters of water, 6 sachets per liter, to be ingested in 3-4 hours); group 2 (36 patients), 90 ml (2 bottles separated approximately 12 hours the day before the colonoscopy) of NaP solution; and group 3 (35 patients) received 1,5 liters of PEG and 45 ml of NaP solutions. Patient tolerance was evaluated after completing the colonic preparation and prior to colonoscopy by means of a nurse-administered questionnaire. Feasibility to complete the preparation, taste and specific symptoms were recorded and scored accordingly. Endoscopists, unawared of the type of preparation, scored the cleansing efficacy in each colonic segment (rectum, sigma, descending, transverse and ascending colon, and cecum). Serum samples were taken for quantification of phosphate and calcium. Endoscopists scored NaP alone as significantly more effective than any of the two PEG-based preparations. The mixed NaP-PEG preparation was easier to accomplish and had fewer side effects than the PEG solution. However, NaP was as safe and significantly easier to accomplish than the mixed NaP-PEG preparation. Hyperphosphatemia was observed in patients taking NaP alone but it did not occur when PEG was associated. Hypocalcemia was never noted. Sodium phosphate as bowel cleansing agent resulted highly effective, easy to accomplish and well tolerated. Serum electrolyte alterations were of little clinical relevance. This side effect can be avoided by associating PEG to NaP, but both efficacy and tolerance decrease. Another conclusion was that PEG-based solutions can not be considered any longer as standard for bowel preparation for colonoscopy.

I hope to have given you the information you requested.

Yours,

Miguel Sobrino-Faya

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A Study on Polyethylene Glycol Electrolyte Lavage Solution and Sodium Picosulfate Combined Pretreatment Method for Colonoscopy

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Summary: As compared to a conventional PEG method, PEG-SP combined method required a less amount of PEG solution to be taken with a reduced pain of the patient involved, allowing a shortened time for examination.

Key words: polyethylene glycol electrolyte lavage solution — sodium picosulfate — colonoscopy — conventional PEG method — PEG-SP combined method

Introduction

A pretreatment method for colonoscopy using a peroral, non-absorptive, non-secretory, enteric lavage solution (Polyethylene Glycol Electrolyte Lavage solution: PEG solution) developed by Glenn R. and Davis et al. in 1980 have widely been employed in Japan with its excellent safety, simplicity and enteric lavage effect so far confirmed. However, a conventional PEG method requires a large amount of ingestion as 2500-3000 ml, imposing not a little burden on the subject to be tested. We recently succeeded to reduce the dose of PEG to 1500 ml to be administered on the day on examination by giving 6 tablets (15 mg) of sodium picosulfate (Laxoberon: SP) on the previous day when no treatment is made in the case of conventional PEG approaches. The usefulness of this PEG-SP method was examined in comparison with that of a conventional PEG method in the present study.

Subjects and Methods

Ninety ambulatory patients experienced a conventional PEG method of PEG-SP combined method for colonoscopy in our outpatient clinic during the period from January 1990 to December 1991 were enrolled in this study. There were 51 males (average age: 52 yrs) and 39 females (56 yrs). Procedure for a conventional PEG method employed in our department was as follows (Table 1): No dietary restriction and medication were performed up to the previous day of examination. On the day of examination, the subject was allowed no food but water and PEG solution was given at a rate of approximately 1000 ml/hr either to a total volume of 2500 ml or till the fecal fluid

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became yellowish or transparent. While in the case of PEG-SP method, 6 SP tablets (15 mg) were given with no dietary restriction on the previous day of examination. On the day of examination, PEG was given at a rate of approximately 1000 ml/hr either to a total volume of 1500 ml or till the fecal fluid became yellowish or transparent.

In addition, the usefulness as well as the time required for attaining initial evacuation of watery feces were compared between conventional PEG method and PEG-SP combined one from the result of a questionnaire survey in the subjects. Furthermore, the degree of enteric lavage was evaluated into 4 grades by an operator at the time of colonoscopy (Table 2). The colonoscopic examination was performed using non-fluoroscopic one man method without anesthesia.

Results

1. Patient's evaluation on a conventional PEG method in comparison with PEG-SP combined method (Table 3)

The result of a questionnaire survey in 30 patients received a conventional PEG method and 60 patients received PEG-SP combined method is described in Table 2. As for the taste, the proportion of subjects answered "drinkable"

TABLE 1.

Composition of PEG per 1,000 ml

Components	weight
Polyethylene glycol	59.10 g
Sodium sulfate (Na_2SO_4)	5.69 g
Sodium bicarbonate ($NaHCO_3$)	1.69 g
Potassium chloride (KCl)	0.74 g
Sodium chloride (NaCl)	1.47 g

TABLE 2.

Degree of enteric lavage

Excellent :	No feces observed
Good :	Required frequent aspirations due to profuse semitransparent residue
Fair :	Observation obstructed by muddy residue
Poor :	Observation being impossible due to profuse feces

TABLE 3.

Patients' total evaluation on a conventional PEG method in comparison with PEG-SP combined by a questionnaire survey

		PEG group	PEG-SP group
Taste	Easily drinkable	23.33% (7/30)	48.33% (29/60)
	Barely drinkable	66.67% (20/30)	46.67% (28/60)
	Undrinkable	10.00% (3/30)	5.00% (3/60)
Volume	Possible to drink more	6.67% (2/30)	43.33% (26/60)
	Drank barely	70.00% (21/30)	51.67% (31/60)
	Too much to drink	23.33% (7/30)	5.00% (3/60)
Complicated symptoms	No symptom	23.33% (7/30)	63.33% (38/60)
	Abdominal distention	53.33% (16/30)	25.00% (15/60)
	Chill	23.33% (7/30)	10.00% (6/60)
	Nausea	30.00% (9/30)	5.00% (3/60)
Frequency of evacuation		7.4±3.51	4.3±2.75

reached more than 90% in both groups. With regard to the dose taken, the proportion of subjects who could drink the test solution up to 1500 ml without pain was as high as 95% in PEG-SP group as compared to 76.67% in PEG group. In addition, as for complicated symptoms due to PEG solution ingested, 63.33% of the subjects in PEG-SP group (up to 1500 ml) had no symptom while abdominal distension, could feeling and/or nausea were complained by 76.66% of those in PEG group (2500 ml), indicating a superiority of the former approach.

2. Enteric lavage effect (Table 4)

The enteric lavage effect was judged according to the criteria shown in Table 3. As a result, the rate of more than effective was almost the same in both groups, 90.00% (27/30) in PEG group and 85.00% (51/60) in PEG-SP group with some retained solution in the large intestine observed in most of these cases. The solution was, however, transparent with no sediment and disappeared by aspiration which provided almost no interference with observation. In addition, obstructed observation due to feces occurred in one case of PEG group but none of PEG-SP group.

TABLE 4.
Enteric lavage effect

	Conventional PEG method	PEG-SP combined method
Excellent	26.67% (8/30)	25.00% (15/60)
Good	63.33% (19/30)	60.00% (36/60)
Fair	6.67% (2/30)	15.00% (9/60)
Poor	3.33% (1/30)	0% (0/60)

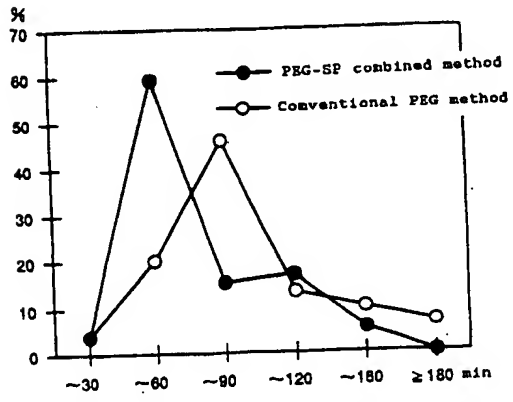

Fig. 1. Time required for attaining initial evaluation of watery feces.

3. Time required for attaining initial evacuation of watery feces (Fig. 1)

On the day of examination, the time elapsed from PEG ingestion to initial evacuation of watery feces was compared between the two groups. In consequence, it was revealed that the time was 102.33± 43.41 min for PEG method and 77.83± 28.80 min for PEG-SP method showing a considerable reduction in time with the latter approach. The proportion of subjects requiring more than 90 min till the initial evacuation of watery feces was 76.67% (23/30) in PEG group and 36.67% (22/60) in PEG-SP group, which clearly indicated a superiority of the latter approach from a view of its rapid onset of effectiveness.

Discussion

In recent years, increased early detection of various colonic disease has been achieved with improved colonoscopic instruments and its techniques. A favorable pretreament approach is thus essential in response to the increased need for colonoscopy. With conventional Brown's modification, however, not only the lavage effect is not adequate in some patients but also the method is complicated requiring dietary restriction and limited daily activities. A lavage solution associated with minimal water and electrolyte absorption or secretion (PEG) was developed by Davis et al. in 1980 and first

introduced in Japan by Ueno et al. in 1985. Since then, this approach has pervaded especially as a pretreatment for colonoscopy. However, its possible fault that requires to ingest a large volume (2500-3000 ml) of lavage solution in a relatively short time may often impose a burden on the patient involved, resulted in a withdrawal of medication due to complicated symptoms such as abdominal distension, chillness feeling and nausea. In order to relieve such a patients' discomfort, some investigators have recently tried to reduce the volume of PEG solu tion to be administered on the day of examination to 2000-2500 ml. This approach, however, still has some problems on its dose and taste. For the purpose of minimizing the patients' discomfort and improving its lavage efficacy while maintaining the simplicity of PEG method, 6 tablets (15 mg) of sodium picosulfate were given on the previous day of examination which succeeded to reduce the dose of PEG solution to 1500 ml on the day of examination.

According to the patients' evaluation on PEG-SP combined method in comparison with a conventional PEG method through a questionnaire survey, 88.33% of the subjects could ingest PEG solution up to 1500 ml with no complicated symptoms, resulted in a reduced burden on the subject involved. However, 11.77% complained of its too much volume to ingest and answered "hard to drink", still remaining a quantitative problem on PEG solution. With regard to the frequency of evacuation, the average value was 7.4 with PEG method and successfully reduced to 4.3 with PEG-SP method. In addition, no patient experienced an anal pain.

The lavage effect of PEG-SP method was good with a comparable efficacy to that of PEG method. The time elapsed from ingestion of PEG solution to initial evacuation of watery feces as an index of simplicity averaged 102.33 min for PEG method and 77.83 min for PEG-SP method indicating a rapid onset of effect with the latter approach which allowed a considerably reduced time required for examination. Since SP has a mild laxative action leading to a enhanced intestinal peristalsis and a suppressed water absorption, evacuation occurred in most cases received PEG-SP on the day of examination. It was thus considered that the lavage effect in the large intestine could be obtained in a relatively short time. Dissimilar to a simultaneous PEG-SP combined method, the intestinal peristalsis was less enhanced during examination and none experienced a necessity of anticonvulsive administration. Futhermore with regard to the safety, Matsumoto et al. (1989) reported that changes in Ht and plasma osmotic pressure after pretreatment of 75 mg (10 ml) SP in aged patients (over 70 yrs) was minimal and thus negligible clinically. In the present study, we also experienced no adverse reactions due to SP administration.

From the results mentioned above, the usefulness of PEG-SP combined method was evident with its excellent simplicity, enteric lavage effect and safety.

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